Translating Scientific Discovery into Better Care: Groundbreaking Research at the National Institute on Aging

Friends of the NIA Briefing

Richard J. Hodes, M.D., Director
Marie A. Bernard, M.D., Deputy Director
National Institute on Aging

May 9, 2018
APPROPRIATIONS & FUNDING
FY18 Budget Status – Funding Increases Across the Board

$37 Billion for the NIH

$500M for Opioids
$140M for BRAIN
$60M for All of US

$414M for AD

• $2.6B for the NIA
• $111M increase for non-targeted NIA research; percent increase comparable to other ICs
• All divisions will benefit
  ➢ DBSR
  ➢ DAB
  ➢ DGCG
  ➢ DN

$37 Billion

$414M for AD
Appropriations

--- | --- | --- | --- | --- | --- | --- | ---
National Alzheimer’s Project Act (NAPA) | $50 M* redirected within NIH budget | $40 M* redirected within NIH budget | $100 M additional approp | $25 M additional approp | $350 M additional approp | $400 M additional approp

*one-year money

Years displayed are Fiscal Years

$414 M in additional appropriations as of 3/23/18
NIA Appropriations

Fiscal Years 2013-2018

Dollars (in millions)

<table>
<thead>
<tr>
<th>Year</th>
<th>NIA Funds</th>
<th>AD Funds</th>
<th>Total</th>
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<td>2018</td>
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NIA Funds  AD funds
Total Active AD/ADRD FOAs

- Basic Research: 20
- Translation: 10
- Clinical Trials: 3
- Caregiving & Clinical Care: 13
- Resource Leverage: 11
- Health Disparities: 4
- Training: 6
New Investigator (NI) and Early Stage Investigator (ESI)
AD/ADRD Awardees FY2015-2017

- R01 and RF1 Awardees: 452
- ESI: 67 (15%)
- Total NI/ESI: 120 (27%)

ESI: Early Stage Investigator
NI: New Investigator
Intramural Research Program

- 10 Intramural Laboratories
- Core facilities
- Home of the BLSA and HANDLS
NIA Laboratory of Neurogenetics

- Found >90% of the genes and risk factors for Parkinson’s disease
- Identified the first rare risk variant for Alzheimer’s disease (TREM2)
- Identified multiple genes for Amyotrophic Lateral Sclerosis and frontotemporal dementia, including the most common cause (c9orf72)
Identified:
• >90% of genes and risk factors for PD
• The first rare risk variant for AD
• The most common disease-causing mutations in ALS and FTD

Created foundational data to link these gene products together, to provide insights regarding biology, mechanisms, and potential druggable targets

Identified:
• A classifier of PD case status that works with 98.7% accuracy at first presentation
• A classifier that detects apparent PD cases that aren’t really PD

Both SNCA level, and LRRK2 kinase activity are in development as targets for PD
Amyloid Deposition is Associated with Motor Impairment Before Cognitive Decline

Division of Aging Biology

- Nathan Shock Centers of Excellence
- Genetics and Cell Biology
  - Genetics
  - Cell Biology
  - Metabolic Regulation
- Aging Physiology
  - Stem cells & Regenerative Biology
  - Immunology
  - Endocrinology
  - Musculoskeletal Biology
  - Tissue Physiology
- Biological Resources
  - Animal Models
  - Biological Resources

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“Geroscience” is the Convergence of Two Fields of Study

Chemotherapy-induced fatigue is diminished by removing senescent cells

*In humans, chemotherapy-induced fatigue correlates positively with senescent cell burden

*In mice, elimination of senescent cells diminishes side effects of chemotherapy

<table>
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<tr>
<th>Toxicity</th>
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<tr>
<td>Cardiac dysfunction</td>
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<td>-</td>
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<tr>
<td>Myelosuppression</td>
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<tr>
<td>Cancer relapse</td>
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TIMP2 from Human Umbilical Cord Plasma Revitalizes Hippocampal Function in Aged Mice

Cognitive Effect

Synaptic Plasticity

Division of Neuroscience

- Basic Neurobiology
- Alzheimer’s Disease
- Sensory Processes
- Learning and Memory
- Sleep
- Cognitive Health

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What Counts as AD/ADRD Research?

• The AD/ADRD payline applies to applications/awards that are coded as AD or Alzheimer’s disease-related dementias (ADRD)

• The ADRD RCDC categories that report related dementias specifically named in the National Plan to Address Alzheimer’s Disease are:
  ➢ Lewy Body dementia (LBD)
  ➢ Frontotemporal dementia (FTD)
  ➢ Vascular Cognitive Impairment/Dementia (VCI/D)
Diversity of AD/ADRD Research

- Aging metabolic changes in AD
- Comparative biology of neurodegeneration
- Basic Biological Processes of AD
- Geroscience
- Research on Disease Mechanisms
- Cognitive outcomes in Population Studies
- Biomarkers
- Research on Care and Caregiver Support
- Disparities, Sex differences, and AD risk
What is CRISPR & How are we using it?

Studying human genes in human brain cells

It’s part of a bacterial defense system that allows us to “edit” a genome

CRISPR/Cas: e.g., APOE3/4, GWAS variants (studies in progress)

Studying human genes in human brain cells

Accelerating Aging:
RFA-AG17-009
e.g., Progerin, ERCC;
CRISPR/Cas TERT, Klotho

CRISPR/Cas:
e.g., APOE3/4,
GWAS variants
(studies in progress)

Studying human genes in human brain cells

Accelerating Aging:
*RFA-AG17-009*
e.g., Progerin, ERCC; CRISPR/Cas TERT, Klotho

Functional Genetics of AD:
*RFA-AG14-012, RFA-AG17-053*

CRISPR/Cas:
e.g., APOE3/4, GWAS variants (studies in progress)

Aducanumab Reduces Amyloid β plaques in AD

Baseline vs One Year for different doses:

- Placebo
- $3 \text{ mg kg}^{-1}$
- $6 \text{ mg kg}^{-1}$
- $10 \text{ mg kg}^{-1}$

Accelerating Medicines Partnership
Alzheimer’s Disease Program

Managing Partner

https://www.nia.nih.gov/alzheimers/amp-ad
Accelerating Medicines Partnership – AD Knowledge Portal

Target Discovery and Preclinical Validation

AMP-AD Knowledge Portal (SAGE)

Predictive Biomarkers in Secondary Prevention Trials

GAAIN
Accelerating Medicines Partnership – AD Knowledge Portal

A hub for data, analysis results, analytical methodology and research tools

Researchers can use it for:

Data Integration (learning from large pools of data)
Predictive Modeling (using what we know to better match compounds to targets)
Molecular Profiling (understanding new targets better)
Experimental Validation (testing interventions in models)

+ Rapid and Broad Sharing (of what we are learning)

https://www.synapse.org/#!Synapse:syn2580853/wiki/409840
"Wall" of Targets - Over 100 novel targets discovered

### AMP-AD Mount Sinai Team

#### Candidate Targets: Preliminary list

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Ongoing NIA AD/ADRD and Related Intervention and Prevention Trials (140+)

40 Early-stage Clinical Drug Development (Phase I and Phase II Clinical Trials)

8 Late-stage Clinical Drug Development (Phase II/III and Phase III Clinical Trials)

62 Non-Pharmacological Interventions

7 Clinical Therapy Development for the Neuropsychiatric Symptoms of AD/ADRD

37 Care and Caregiver Interventions

Amyloid (9)
Neurotransmitter Receptors (3)
Metabolism and Bioenergetics (4)
Vasculature (3)
Growth Factors and Hormones (1)
Multi-target (6)
Oxidative Stress (1)

Amyloid (6)
Vasculature (2)

Exercise (16)
Diet (2)
Cognitive Training (20)
Combination Therapy (11)

Pharmacological (5)
Non-Pharmacological (2)
Early Intervention May Be Possible – Thanks to Trial Volunteers from a Colombian Family

Fleisher, AS et al. (2012). Lancet Neurology

Non-Carriers, late 30’s

Gene Carriers, late 30’s

Dementia onset is in late 40’s

Beta-amyloid, late 20’s

Fleisher, AS, Reiman, EM and colleagues (2012). Lancet Neurology
Challenges for AD/ADRD Studies

• Lack of eligibility
• Lack of capacity, awareness and resources among primary care providers
• Study partner requirements
• Invasive procedures
• Need for pre-symptomatic volunteers
• Barriers for underrepresented communities
• National Recruitment Strategy in development – for release in the summer of 2018
The framework will hopefully aid researchers in identifying individuals at risk for disease sufficiently early to test new prevention strategies as they emerge.

division of behavioral and social research

• Elucidating causal links between behavioral and social factors and aging trajectories
• Explaining and reducing disparities in health at older ages
• Reversing or mitigating effects of early-life risk factors
• Improving dementia care and health of caregivers
• Behavioral interventions and preventing disability

c/o Gerontology Society of Iowa

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Higher Physician Spending is Not Associated with Lower Mortality or Hospital Readmission

Life expectancy in US is 78.8 years, falling short of OECD average of 80.5 years.

There is substantial variation in health care spending across US – is spending associated with outcomes?

Spending varies more across individual physicians rather than hospitals, and higher physician spending is not associated with better outcomes for patients.

Tsugawa Y et al. (2017) JAMA Intern Med 177(5):675-682
Childhood Abuse Increases Mortality Rates in Women

Some Approaches used in Behavioral and Social AD/ADRD Research

- Prevention
  - Interventions on behavioral risk factors
  - Cognitive training

- Dementia Care
  - Care/non-pharmacologic interventions for persons living with dementia
  - Neighborhood and social factors

- Caregiver Research and Interventions
  - Caregiver depression, burden, self-care and social support
  - Economics of caregiving

- Disparities
  - Investigate disparities based on race, ethnicity, gender, place (e.g. rural) in dementia care studies and epidemiology

- Early Psychological Changes in AD
  - Affective function
  - Decision-making
  - Social function

- Behavioral and Social Pathways to AD/ADRD
  - Educational attainment
  - Personality
  - Social engagement

- Epidemiology
  - Prevalence, incidence, burden of illness
  - Cross-national comparisons
Cognitively healthy life span has increased as much as life span

Adapted from Crimmins, E. et al. (2016). *SSM Popul Health* 2: 793-797.
Poor Caregiver Mental Health Predicts Mortality of Patients with Neurodegenerative Disease

Caregiving Research: More Active than Ever

- Integration of recommendations from the 2017 Care/Services Summit into FY2020 AD/ADRD Bypass Budget Planning:
  

- Funding opportunity announcements already released

- Next Care/Services Summit dates: March 24-25, 2020

- Planned systematic review of care/caregiving interventions – what’s ready for prime time?
Division of Geriatrics and Clinical Gerontology

- Maintaining health and independence in old age
- Improving functional abilities in old age
- Coexisting conditions
- Aging across the life span; exceptionally healthy aging
- Aging mechanisms influencing health span and longevity
- Clinical trials: Prevention and treatment

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Diet and/or Exercise to Treat Heart Failure with Preserved Ejection Fraction

Falling when a knee buckled at baseline

Association of knee buckling without a fall and buckling with a fall at baseline with falls and fall injuries at 84 months

SPRINT Study

Hazard ratio with intensive treatment, 0.75 (95% CI, 0.64–0.89)

Standard treatment

Intensive treatment

Years

Inclusion Across the Lifespan Policy Update
Timeline of NIH Inclusion Policies and Participant Data Collection

1986
- NIH establishes policy encouraging researchers to include women in studies

1993
- PL103-43 requires inclusion of women and minorities in NIH clinical research

1998
- NIH issues policy requiring inclusion of children in NIH clinical research

2002
- NIH issues notice changing definition of child from individuals under 21 to under 18

2015
- NIH issues notice changing definition of child from individuals under 21 to under 18

2016
- 21st Century Cures Act includes new requirements on age of participants in NIH Clinical Research
Summary of Key Findings in Older Adult Inclusion

• For diseases highly prevalent among older people, clinical trials often excluded subjects based on age
  • 27% of studies had arbitrary upper age caps

• Indirect exclusion factors may apply
  • Co-morbid conditions (hypertension, diabetes, cancer, etc.)
  • Polypharmacy

• Participants in trials may not represent real-world populations with the disease
Requires NIH to:

1. Convene a workshop on age groupings and age exclusions in clinical research within 180 days of enactment
   • Post workshop findings on NIH website
2. Publish data on age of participants in NIH clinical research, including pediatric subgroups
3. NIH Director must determine whether the inclusion guidelines on age need revision within 180 days of the workshop
Purpose: To discuss the challenges and barriers to including children and older adults in clinical research and to identify strategies that would produce more age-inclusive clinical studies.
Inclusion Across the Lifespan
Working Groups


www.report.nih.gov
Inclusion Policy Developments Continued

• NOT-OD-18-116: Revision: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects (12/19/17)


Changes to the policy include:

(1) the applicability of the policy to individuals of all ages, including children and older adults
(2) clarification of potentially acceptable reasons for excluding participants based on age
(3) a requirement to provide data on participant age at enrollment in progress reports.
Inclusion Across the Lifespan: Guidance for Applying the Policy

In applications or proposals:
Include an Inclusion plan
- Submit a plan for including individuals across the lifespan
- If excluding based on age, provide rationale and justification for the specific age range*

In progress reports:
Report age at enrollment
- The policy requires the age of participants at enrollment, sex/gender, and race/ethnicity be included in reports.
- Age at enrollment may be reported to NIH in units ranging from hours to years.

Remember: Scientific Review Groups (SRGs) will assess each application/proposal as being “acceptable” or “unacceptable” with regard to the age-appropriate inclusion or exclusion of individuals in the research project.
Put some spring in your step!

STAY ACTIVE

Be Active Every Day!
go4life.nia.nih.gov/month
Stay Connected with the NIA

Get free info on aging, health & Alzheimer’s disease

Aging & Health Info
• www.nia.nih.gov/health
• www.nia.nih.gov/espanol

Alzheimer’s Disease Education & Referral Center
• www.nia.nih.gov/alzheimers

Inside NIA Blog
• https://www.nia.nih.gov/research/blog